IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

BAYER HEALTHCARE AG, et al., Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Civil Action No. 06-234-SLR Civil Action No. 07-195-SLR CONSOLIDATED CASES **REDACTED PUBLIC VERSION**

FIRST AMENDED ANSWER AND AFFIRMATIVE DEFENSES OF DEFENDANT TEVA PHARMACEUTICALS USA, INC.
CIVIL ACTION NO. 06-234-SLR

Defendant Teva Pharmaceuticals USA, Inc. ("Teva USA"), by and through its attorneys, hereby answers the Complaint in this action as follows:

1. Teva USA admits this is an action for patent infringement under the patent laws of the United States, Title 35, United States Code, that arises out of the filing by Teva USA with the U.S. Food and Drug Administration, Teva USA's Abbreviated New Drug Application ("ANDA") No. 78-073 for "Moxifloxacin Hydrochloride Ophthalmic Solution" to obtain approval to engage in the commercial manufacture, use or sale of the drug product before the expiration of U.S. Patents 4,990,517, 5,607,942 and 6,716,830, and their pediatric exclusivities. Teva USA denies the remaining allegations of paragraph 1 of the Complaint.

2. Teva USA is without knowledge or information sufficient to form a belief as to the truth of the allegations set forth in paragraph 2 of the Complaint, and therefore denies them.

3. Teva USA is without knowledge or information sufficient to form a belief as to the truth of the allegations set forth in paragraph 3 of the Complaint, and therefore denies them.

4. Teva USA is without knowledge or information sufficient to form a belief as to the truth of the allegations set forth in paragraph 4 of the Complaint, and therefore denies them.

5. Admitted.

6. Admitted.

7. Admitted for the purpose of this action only.

8. Teva USA incorporates its Answer to each of the preceding Paragraphs 1-7 as if fully set forth herein.

9. Teva USA admits that United States Patent No. 4,990,517 ("the '517 patent") issued on February 5, 1991 and that the '517 patent bears the title "7-(1-Pyrrolidinyl)-3-Quinolone- And -Naphthyridonecarboxylic Acid Derivatives As Antibacterial Agents And Feed Additives." Teva USA is without sufficient information as to the truth of the allegation regarding the assignment of the '517 patent, and Teva USA denies the remaining allegations in paragraph 9 of the Complaint.

10. Teva USA admits that United States Patent No. 5,607,942 ("the '942 patent") issued on March 4, 1997 and that the '942 patent bears the title "7-(1-Pyrrolidinyl)-3-Quinolone-And -Naphthyridone-Carboxylic Acid Derivatives As Antibacterial Agents And Feed Additives." Teva USA is without sufficient information as to the truth of the allegation regarding the assignment of the '942 patent, and Teva USA denies the remaining allegations in paragraph 10 of the Complaint.

11. Teva USA is without sufficient knowledge or information to form a belief as to the truth of the allegations set forth in paragraph 11 of the Complaint, and therefore denies them.

12. Teva USA is without sufficient information to form a belief as to the truth of the allegation that Plaintiff Bayer HealthCare AG ("BHC") owns both the '517 patent and the '942 patent, and Teva USA denies the remaining allegations in paragraph 12 of the Complaint.

13. Teva USA admits that it sent a letter dated February 21, 2006 to Bayer Healthcare, Pharmaceutical Division, Bayer HealthCare AG, Alcon Pharmaceuticals, Ltd., and Alcon Laboratories, Inc. to notify each of them that Teva USA had submitted its ANDA for Moxifloxacin Hydrochloride Ophthalmic Solution, and to inform them that Teva USA sought to obtain approval of its drug product prior to the expiration of the '517 patent, the '942 patent, the '830 patent, and their pediatric exclusivities. Teva USA denies the remaining allegations of paragraph 13 of the Complaint.

14. Teva USA denies each and every allegation in paragraph 14 of the Complaint.

15. Teva USA admits that it notified Bayer HealthCare AG, Bayer Healthcare, Pharmaceutical Division, Alcon Pharmaceuticals Ltd., and Alcon Laboratories, Inc. that, as part of its ANDA, Teva had filed certifications of the type described in Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

16. Teva USA denies the allegations of paragraph 16 of the Complaint as stated but admits that its submission of ANDA No. 78-073 creates a cause of action for infringement in the patent holders of the '517, '942 and '830 patents.

17. Teva USA denies each and every allegation in paragraph 17 of the Complaint.

18. Teva USA denies each and every allegation in paragraph 18 of the Complaint.

19. Teva USA incorporates its Answers to each of paragraphs 1-7 of the Complaint as if fully set forth herein.

20. Teva USA admits that United States Patent No. 6,716,830 ("the '830 patent") issued on April 6, 2004 and that the '830 patent bears the title "Ophthalmic Antibiotic Compositions Containing Moxifloxacin." Teva USA is without sufficient information as to the truth of the allegations regarding the assignment of the '830 patent and Teva USA denies the remaining allegations in paragraph 20 of the Complaint.

21. Teva USA is without sufficient information as to the truth of the allegation that Alcon, Inc. owns the '830 patent. Teva USA admits that Alcon, Inc. appears to hold an approved New Drug Application for VIGAMOX®. Teva USA denies the remaining allegations in paragraph 21 of the Complaint.

22. Teva USA is without sufficient information as to the truth of the allegation that Alcon Manufacturing, Ltd. has been granted an exclusive license under the '830 patent. Teva USA denies the remaining allegations in paragraph 22 of the Complaint.

23. Teva USA admits that it sent a letter dated February 21, 2006 to Bayer Healthcare, Pharmaceutical Division, Bayer HealthCare AG, Alcon Pharmaceuticals Ltd., and Alcon Laboratories, Inc. to notify each of them that Teva USA had submitted its ANDA for Moxifloxacin Hydrochloride Ophthalmic Solution, and to inform them that Teva USA sought to obtain approval of its drug product prior to the expiration of the '517 patent, the '942 patent and the '830 patent, and their pediatric exclusivities. Teva USA denies the remaining allegations of paragraph 23 of the Complaint.

24. Teva USA denies each and every allegation in paragraph 24 of the Complaint.

25. Teva USA admits that it notified Bayer HealthCare AG, Bayer Healthcare, Pharmaceutical Division, Alcon Pharmaceuticals Ltd., and Alcon Laboratories, Inc. that, as part

of its ANDA, Teva had filed certifications of the type described in Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

26. Teva USA denies each and every allegation in paragraph 26 of the Complaint.

27. Teva USA denies the allegations of paragraph 27 of the Complaint as stated but admits that its submission of ANDA No. 78-073 creates a cause of action for infringement in the patent holders of the '517, '942 and '830 patents.

28. Teva USA denies each and every allegation in paragraph 28 of the Complaint.

FIRST AFFIRMATIVE DEFENSE

29. The drug product for which Teva USA has filed its Abbreviated New Drug Application (ANDA) will not infringe any valid claim of any of the '517, '942, or '830 patents.

SECOND AFFIRMATIVE DEFENSE

30. The '517 patent and each of the claims allegedly infringed by Teva USA are invalid for failure to comply with one or more of the conditions of patentability specified in 35 U.S.C. §§ 101, 102, 103, and/or 112.

31. The '942 patent and each of the claims allegedly infringed by Teva USA are invalid for failure to comply with one or more of the conditions of patentability specified in 35 U.S.C. §§ 101, 102, 103, and/or 112.

32. The '830 patent and each of the claims allegedly infringed by Teva USA are invalid for failure to comply with one or more of the conditions of patentability specified in 35 U.S.C. §§ 101, 102, 103, and/or 112.

33. Pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV), Teva USA's ANDA included a certification with respect to the '517, '920, and '830 patents. Pursuant to 21 U.S.C. § 355(j)(2)(B)(iii) and (iv), Teva USA also provided each of the Bayer Healthcare, Pharmaceutical

Division, Bayer Healthcare AG, Alcon, Inc., and Alcon Manufacturing Ltd. ("Plaintiffs") with a detailed statement of the factual and legal basis of Teva USA's opinion regarding the invalidity, unenforceability or noninfringement of the claims of the '517, '942, and '830 patents.

34. Pursuant to 21 U.S.C. § 355 (j)(5)(C)(i)(III) Teva USA made an offer of Confidential Access to Plaintiffs of Teva USA's ANDA for the purpose of allowing Plaintiffs to determine whether to bring an action against Teva USA. Plaintiffs ignored Teva USA's offer and filed suit without availing themselves of the opportunity to fully investigate Teva USA's ANDA prior to filing suit.

35. Given Teva USA's detailed statement and the information and materials that Teva USA offered to provide to Plaintiffs, no reasonable litigant could expect success on the merits of this patent infringement action against Teva USA.

WHEREFORE, Teva USA requests entry of a judgment:

A. Dismissing Plaintiffs' Complaint with prejudice;

B. Denying all relief requested by Plaintiffs and any relief to Plaintiffs whatsoever;

C. That Teva USA has not infringed and is not infringing any valid and enforceable claim of the '517, '942, or '830 Patents;

D. Awarding Teva USA reasonable attorney's fees pursuant to, *inter alia*, 35 U.S.C. § 285;

E. Awarding Teva USA its costs of this action; and

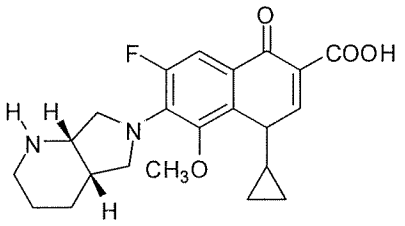
F. Awarding Teva USA such additional relief as this Court Deems just and proper.

THIRD DEFENSE – INEQUITABLE CONDUCT

36. On March 20, 1995 U.S. Patent Application 08/406,448 (hereinafter "the '448 application") was filed in the name of Uwe Petersen et al.

37. As of July 20, 1995, the '448 application had not been examined by the United States Patent and Trademark Office (PTO). However, the applicants had submitted preliminary amendments in order to obviate an expected obviousness-type double patenting rejection made in connection with U.S. Patent Application 08/026,906.

38. As of July 20, 1995, claim 25 of the '448 application recited as follows:

> 25. The compound 1-cyclopropyl-7-([S,S]-2,8-diazabicyclo-[4.3.0]non-8-yl)-6-fluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid having the formula:
>
> 
>
>
> or an alkali metal, alkaline earth metal, silver or guanidinium salt thereof or a pharmaceutically utilizable hydrate or acid addition salt thereof, said compound substantially free of other enantiomers and stereoisomers.

39. On July 20, 1995, Dr. Klaus-Dieter Bremm (hereinafter "Dr. Bremm") executed a declaration (hereinafter "the Bremm declaration") in connection with the '448 application.

40. The Bremm declaration was filed in the PTO on or about September 21, 1995, with a third preliminary amendment, in connection with the '448 application.

41. A copy of the Bremm declaration is attached hereto as Exhibit A.

42. Dr. Bremm consulted with Dr. Uwe Petersen in drafting the Bremm declaration.

43. Dr. Bremm drafted all sections of the Bremm declaration except paragraph 6.

44. Dr. Bremm intended the Bremm declaration to respond to questions raised by the PTO in connection with the examination of the '448 application.

45. The Bremm declaration states: "of all of the fluoroquinolones that we have investigated, the compound of claim 25 is the best tolerated that we have ever seen."

46. As of July 20, 1995, Dr. Bremm knew that {REDACTED].

47. As of July 20, 1995, Dr. Bremm knew {REDACTED].

48. {REDACTED}.

49. In June 1993, Dr. Bremm participated in a meeting at Bayer, during which {REDACTED}.

50. Minutes of the June 1993, meeting referred to in paragraph 49 are attached hereto as Exhibit B.

51. Dr. Bremm received a copy of the minutes attached hereto as Exhibit B.

52. The minutes attached hereto as Exhibit B indicate that {REDACTED}.

53. As of July 20, 1995, Dr. Bremm knew that {REDACTED}.

54. As of July 20, 1995, Dr. Bremm knew that {REDACTED}.

55. As of July 20, 1995, Dr. Bremm knew that {REDACTED}.

56. Dr. Bremm intended the Bremm declaration to inform the PTO of {REDACTED}.

57. Dr. Bremm did not inform the PTO of {REDACTED}.

58. Dr. Bremm intended not to inform the PTO of {REDACTED}.

59. {REDACTED} was material to the patentability of the '448 application.

60. Dr. Bremm did not inform the PTO of {REDACTED}.

61. Dr. Bremm intended not to inform the PTO of {REDACTED}.

62. {REDACTED} were material to the patentability of the '448 application.

63. By not disclosing {REDACTED}, the Bremm declaration misrepresented the superior tolerability of "the compound of claim 25" based only on {REDACTED}.

64. According to an Examiner Interview Summary Record for an interview on July 1, 1996, the Examiner at the PTO agreed that the "showing of unexpected results overcomes the obviousness-type rejection."

65. On July 18, 1996, the Examiner at the PTO issued a Notice of Allowance for the '448 application.

66. The '448 application issued as U.S. Patent 5,607,942 (hereinafter "the '942 patent") on March 4, 1997.

67. Dr. Bremm's intentional failure to inform the PTO of the {REDACTED} breached his duties under 37 C.F.R. § 1.56.

68. Dr. Bremm's intentional failure to inform the PTO of {REDACTED} amounted to inequitable conduct.

69. Dr. Bremm's intentional failure to inform the PTO of {REDACTED} breached his duties under 37 C.F.R. § 1.56.

70. Dr. Bremm's intentional failure to inform the PTO of {REDACTED} amounted to inequitable conduct.

71. Dr. Bremm's intentional misrepresentation of the superior tolerability of "the compound of claim 25" based only on {REDACTED} breached his duties under 37 C.F.R. § 1.56.

72. Dr. Bremm's intentional misrepresentation of the superior tolerability of "the compound of claim 25" based only on {REDACTED} amounted to inequitable conduct.

WHEREFORE, Teva USA requests entry of a judgment:

A. That '942 patent was obtained through Dr. Bremm's inequitable conduct;

B. That, as a result of the inequitable conduct, the '942 patent is unenforceable;

C. That Bayer's assertion of an unenforceable patent renders this an "exceptional case" in accordance with 35 U.S.C. § 285;

D. That Teva be awarded costs and attorneys' fees; and

E. That Teva be awarded such other relief as the Court finds just and equitable.

FOURTH DEFENSE – INEQUITABLE CONDUCT

73-79. Teva repeats and realleges the allegations stated in paragraphs 36-42 to the same extent as if they were separately stated in paragraphs 73-79.

80. Dr. Bremm was asked by Dr. Petersen, the first named inventor of the '448 application, to provide the PTO with additional information on some of the compounds of the '448 application.

81. Dr. Petersen intended the Bremm declaration to respond to questions raised by the PTO in connection with the examination of the '448 application.

82. The Bremm declaration states: "of all of the fluoroquinolones that we have investigated, the compound of claim 25 is the best tolerated that we have ever seen."

83. Dr. Petersen assisted Dr. Bremm in drafting the language quoted in paragraph 82.

84. As of July 20, 1995, Dr. Petersen knew that {REDACTED}.

85. As of July 20, 1995, Dr. Petersen knew {REDACTED}.

86. As of July 20, 1995, Dr. Petersen knew that {REDACTED}.

87. Upon information and belief, in June 1993, Dr. Petersen participated in a meeting at Bayer, during which {REDACTED}.

88. Minutes of the June 1993, meeting referred to in paragraph 87 are attached hereto as Exhibit B.

89. On information and belief, Dr. Petersen received a copy of the minutes attached hereto as Exhibit B.

90. The minutes attached hereto as Exhibit B indicate that {REDACTED}.

91. As of July 20, 1995, Dr. Petersen knew that {REDACTED}.

92. As of July 20, 1995, Dr. Petersen knew that {REDACTED}.

93. Dr. Petersen knew that the Bremm declaration did not inform the PTO of {REDACTED}.

94. Dr. Petersen intended not to inform the PTO of {REDACTED}.

95. Dr. Petersen intended for the Bremm declaration not to inform the PTO of {REDACTED}.

96. {REDACTED} was material to the patentability of the '448 application.

97. Dr. Petersen knew that the Bremm declaration did not inform the PTO that {REDACTED}.

98. Dr. Petersen intended not to inform the PTO that {REDACTED}.

99. Dr. Petersen intended for the Bremm declaration not to inform the PTO that {REDACTED}.

100. {REDACTED} was material to the patentability of the '448 application.

101. Dr. Petersen intended not to inform the PTO of {REDACTED}.

102. Dr. Petersen intended for the Bremm declaration not to inform the PTO of {REDACTED}.

103. {REDACTED} were material to the patentability of the '448 application.

104. According to an Examiner Interview Summary Record for an interview on July 1, 1996, the Examiner at the PTO agreed that the "showing of unexpected results overcomes the obviousness-type rejection."

105. On July 18, 1996, the Examiner at the PTO issued a Notice of Allowance for the '448 application.

106. The '448 application issued as U.S. Patent 5,607,942 (hereinafter "the '942 patent") on March 4, 1997.

107. Dr. Petersen's intentional failure to inform the PTO of {REDACTED} breached his duties under 37 C.F.R. § 1.56.

108. Dr. Petersen's intentional failure to inform the PTO of {REDACTED} amounted to inequitable conduct.

109. Dr. Petersen's intentional failure to inform the PTO that {REDACTED} breached his duties under 37 C.F.R. § 1.56.

110. Dr. Petersen's intentional failure to inform the PTO that {REDACTED} amounted to inequitable conduct.

111. Dr. Petersen's intentional failure to inform the PTO of {REDACTED} breached his duties under 37 C.F.R. § 1.56.

112. Dr. Petersen's intentional failure to inform the PTO of {REDACTED} amounted to inequitable conduct.

WHEREFORE, Teva USA requests entry of a judgment:

A. That the '942 patent was obtained through Dr. Petersen's inequitable conduct;

B. That, as a result of the inequitable conduct, the '942 patent is unenforceable;

C. That Bayer's assertion of an unenforceable patent renders this an "exceptional case" in accordance with 35 U.S.C. § 285;

D. That Teva USA be awarded costs and attorneys' fees; and

E. That Teva USA be awarded such other relief as the Court finds just and equitable.

August 3, 2007

OF COUNSEL:

Bruce M. Gagala
M. Daniel Hefner
Brian A. Garcia
Douglas A. Robinson
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
Chicago, Illinois 60601

THE BAYARD FIRM

/s/ Richard D. Kirk (rk0922)
Richard D. Kirk
Ashley B. Stitzer
222 Delaware Avenue, Suite 900
P.O. Box 25130
Wilmington, Delaware 19899
(302) 655-5000
rkirk@bayardfirm.com

Attorneys for Defendant,
TEVA PHARMACEUTICALS USA, INC.

CERTIFICATE OF SERVICE

The undersigned counsel certifies that, on August 3, 2007, he electronically filed the foregoing document with the Clerk of the Court using CM/ECF, which will send automatic notification of the filing to the following:

Frederick L. Cottrell III, Esquire
Jeffrey L. Moyer, Esquire
Anne Shea Gaza, Esquire
Richards, Layton & Finger, P.A.
One Rodney Square
920 North King Street
Wilmington, Delaware 19801

The undersigned counsel further certifies that, on August 3, 2007, copies of the foregoing document were sent by email and hand to the above local counsel and by email and first class mail to the following non-registered participant:

Bruce R. Genderson, Esquire
Adam L. Perlman, Esquire
Dov P. Grossman, Esquire
David I. Berl, Esquire
Aaron P. Maurer, Esquire
Williams and Connolly
725 Twelfth Street, N.W.
Washington, D.C. 20005

/s/ Richard D. Kirk (rk0922)
Richard D. Kirk

EXHIBIT A

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Le A 26 108-US-04-div PB/ge

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	UWE PETERSEN ET AL.
Serial No.	:	08/406,448
Filed	:	March 20, 1995
For	:	7-(2,8-DIAZABICYCLO[4.3.0]NON-8-YL)-3-QUINOLONE-AND NAPHTYRIDONE-CARBOXYLIC ACID DERIVATIVES AS ANTIBACTERIAL AGENTS AND FEED ADDITIVES
Group Art Unit	:	1202
Examiner	:	P. Datlow

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION OF KLAUS-DIETER BREMM PURSUANT TO 37 CFR §1.132

Sir:

I, KLAUS-DIETER BREMM, of Eberhardstraße 20, 45661 Recklinghausen, Germany, a citizen of Germany, hereby declare:

1. On December 2, 1994, I executed a declaration in connection with U.S. Serial No. 08/026,906 (hereinafter "my previous declaration") that reported the results of comparisons

involving the compound of instant claim 25 ("X=OCH_3") and the closely related 8-Cl ("X=Cl") and 8-F ("X=F") analogs thereof;

2. My qualifications to make this declaration are readily apparent from numbered paragraphs 1-5 of my previous declaration;

3. I have studied the Advisory Action in U.S. Serial No. 08/026,906 dated January 13, 1995, wherein the Examiner finds that a reduced phototoxicity is relevant to the intended pharmaceutical use as an antimicrobial, but also finds that:

(i) there is no evidence that the tests set forth in the declaration are standard tests for phototoxicity of pharmaceuticals; and

(ii) it is not clear that the improved results shown in the declaration for the claimed compound would translate into practical benefits when the claimed compound is used in a patient;

4. With respect to point (i), accompanying this declaration is an Information Disclosure Statement including

excerpts from the well known text Toxicology: The Basic Science of Poisons, M. O. Amdur et al., editors, fourth edition, McGraw-Hill, Inc., New York (1993).

The first paragraph of the section bridging pages 476-477 defines "photosensitization reactions" as "abnormal adverse reactions to ultraviolet (UV) and/or visible radiation." It is stated that phototoxicity and photoallergy are the most important of these photosensitization reactions.

That same paragraph defines "photoxicity" as "a chemically induced increased reactivity of a target tissue to UV and/or visible radiation on a nonimmunologic basis."

The first full paragraph on page 477 teaches that the skin and the eyes are the major organs affected by phototoxic reactions.

My previous declaration reported that the in vivo photoxic potential of the tested quinolones was evaluated in guinea pigs.

Guinea pigs are commonly used to evaluate sensitization

reactions. See the text Toxicology in the middle of the left-hand column on page 33.

In our own laboratory, we have confirmed the correlation between the guinea pig model and the situation in vivo in humans.

In this regard, the compound having X = Cl is also designated "Bay Y 3118" within our company.

This compound Bay Y 3118 was developed to the point of phase I clinical trials in healthy human volunteers.

The phototoxic potential of this compound had previously been evaluated in mice and rats. However, the evaluation did not reveal any remarkable phototoxic potential for Bay Y 3118.

However, serious phototoxic problems were revealed during the phase I clinical trials. As a consequence, the development of Bay Y 3118 was terminated.

In this regard, in connection with our application for

approval of Bay Y 3118 in Japan, we were requested by the Japanese authorities to provide phototoxicity test data in guinea pigs.

It was when we attempted to gather this data that we first discovered the high phototoxic potential of this compound. The guinea pig model yielded a "no effect level (NOEL)" of 1 mg/kg for Bay Y 3118.

Simultaneously, phototoxicity tests in humans were conducted by J. Ferguson of the University of Dundee in Scotland. These tests also confirmed that Bay Y 3118 had an extraordinarily high phototoxicity potential.

The suitability of this model was also confirmed by comparing the guinea pig and human phototoxic responses with other known quinolones including ciprofloxacin, lomefloxacin and sparfloxacin (see results from BAYER, Department of Toxicology). In these comparisons, the results in guinea pigs reflected quite well the results in humans.

Further proof of the acceptability of the guinea pig phototoxicity model is apparent from the article by M. Furukawa

et al. in Iyakuhin Kenkyu, 21(5), 989-97 (1990), which is also included in the accompanying Information Disclosure Statement. It should be clear from the abstract and the accompanying English language translation that the phototoxicity study was carried out in guinea pigs.

5. With respect to point (ii), a practical benefit is clearly expected when the activity of the claimed compound is compared to that of the commercial standard, ciprofloxacin, for instance.

Ciprofloxacin is sold in the form of 500 mg tablets. The recommended schedule is for the patient to take 3 tablets per day, i.e., a total intake of 1500 mg per day. This schedule presumes that the weight of the average patient is 75 kg. Therefore, the average daily intake is 1500 mg/75 kg/day = 20 mg/kg/day. This calculates to 6-7 mg/kg/dose.

The Staphylococcus aureus-infected mouse model is a well known and widely accepted animal model for antibacterial activity. See the U.S. patents cited in the accompanying Information Disclosure Statement.

It is my experience that the results in the Staphylococcus aureus-infected mouse model correlate quite well to the situation in vivo in humans.

The protocol varies slightly from laboratory to laboratory, but, in our laboratory, the protocol for this test is as follows:

Overnight cultures of *S.aureus* were diluted and incubated for additional two hours to insure that the organisms were in the logarithmic phase of growth. These cultures were then diluted in 0,9% NaCl for injection $5x10^6$/0.2 ml *S.aureus* (strain 133)bacteria into the peritoneal cavity of mice. Infected animals were treated once, 0.5 hours after infection. Survival of the mice was documented up to the 6th post infection day. The dosage which gave ≥90% survival was protocolled as active.

In this test, the ciprofloxacin and the compounds set forth in my previous declaration exhibited the following activities:

Table: Activity (≥90% survival) in Staphylococcus aureus infection in the mouse (mg/kg)

Compound	Oral (p.o.)	Subcutaneous (s.c.)
Ciprofloxacin	80	80
X = OCH_3	10	10
X = Cl	5	5
X = F	10	5

It should be clear that at a minimum the compounds in my previous declaration were 8 times as active as ciprofloxacin. As I noted above, the activities in this model correlate well to the situation in vivo in humans. Therefore, it would have been expected that a useful in vivo dosage for the compounds in my previous declaration would be 1/8 that of ciprofloxacin, which calculates to approximately 2-3 mg/kg/day or approximately 1 mg/kg/dose.

Now, consider the data in Table I on page 4 of my previous declaration. The data in vivo in guinea pigs for the compounds wherein X = Cl or F show systemic phototoxic effects and/or local phototoxic effects occur with in vivo dosages above 3 mg/kg and 1.5 mg/kg, respectively. In other words, at approximately the dosage levels required to produce a beneficial

effect, these compounds also show some phototoxic effects.

By way of contrast, the phototoxicity threshold for the compound having X = OCH_3 is much higher, i.e., > 100 mg/kg. In other words, at the dosage levels required to produce a beneficial effect with this compound, there is no phototoxic effect.

Indeed, of all of the fluoroquinolones that we have investigated, the compound of claim 25 is the best tolerated that we have ever seen.

In closing, I would repeat for emphasis certain statements from my previous declaration:

> "The compound wherein X = OCH_3 has a much better pharmacological profile than do the corresponding compounds wherein X = Cl or F. In practical terms, this means that the compound wherein X = OCH_3 can be given to patients in slightly higher dosages, will kill the same amount of bacteria and, moreover, will still be better tolerated by the patient than will be the corresponding compounds wherein X = Cl or F.
>
> The results are surprising and unexpected in my view. U.S. Patent No. 4,990,517 clearly suggests at column 3, line 37, through column 4, line 35, that compounds wherein X = Cl or F are the best overall

('particularly preferred'). Further support for this position can be taken from species claims 4 - 7 of the patent, which all have either X = Cl or F. Consequently, the present discovery that the instant compound having X = OCH_3 has a much better pharmacological profile than do the corresponding compounds wherein X = Cl or F is surprising and unexpected and indicative of nonobviousness."

6. I hereby declare that all statement made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 20.7.95 By KD Bremm

Klaus-Dieter Bremm

EXHIBIT B
This document is confidential under the Protective Order
and has been filed under seal.